# UNITED STATES PATENT AND TRADEMARK OFFICE

## BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte CHIN-WEN CHI, HENG-LIANG LIN, TSUNG-YUN LIU, WING-YIU LUI and GAR-YANG CHAU

Appeal No. 2006-0674
Application No. 10/083,565



ON BRIEF

Before SCHEINER, ADAMS and GREEN, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims directed to treatment of hepatocellular carcinoma by intravenous administration of docetaxel. The examiner has rejected claims 7-9, 12 and 16-22 as obvious over the prior art. Claims 13-15 are also pending, but have been withdrawn from consideration. We have jurisdiction under 35 U.S.C. § 134. We find that the examiner has not established a prima facie case of unpatentability, and reverse the rejection.

## Background

"Hepatocellular carcinoma (HCC) is one of the most common cancers in Southeast Asia and African countries . . . [and] [t]he survival rate of HCC patients is very low." Specification, page 1. Paclitaxel, an antimitotic drug isolated from the bark of Yew trees, "inhibits tumour cell division by its action on microtubule assembly" and is "cell cycle dependent, with cell cycle arrest occurring mainly at the G2/M phase" (id.). "Recent studies have shown that paclitaxel is effective against various malignant tumour cells such as brain tumour, gastric and prostate cancer, breast cancer, melanoma and ovarian cancer" (id.), but "paclitaxel is not effective against hepatocellular carcinoma" (id.).

Docetaxel is a semisynthetic taxoid structurally similar to paclitaxel. However, according to appellants, "docetaxel can achieve non cell cycle dependent cytotoxicity in HCC cells[,] . . . "indicat[ing] that the cytotoxic effect of docetaxel on HCC cells is achieved by a different mechanism from that of paclitaxel" (id.). "Further, the in vitro activity of docetaxel against HCC cells is significantly higher than that of paclitaxel at concentrations of up to 1μM . . . suggest[ing] that docetaxel, unlike paclitaxel, will be of practical use in the clinical treatment of hepatocellular carcinoma" (id.).

## The Claims

Claims 7-9, 12 and 16-22 are on appeal. Claim 7, the only independent claim on appeal, is representative:

7. A method of treating hepatocellular carcinoma, said method comprising administering to a patient docetaxel in an amount sufficient to treat said hepatocellular carcinoma, wherein said administering is intravenous.

Thus, the claims require intravenous administration of docetaxel to a patient with hepatocellular carcinoma, in an amount sufficient to treat the hepatocellular carcinoma.

Discussion

The examiner rejected claims 7-9, 12 and 16-22 under 35 U.S.C. § 103 as unpatentable in view of Broder.[1] Broder teaches that "[m]any valuable pharmacologically active compounds cannot be effectively administered by the oral route because of poor systemic absorption from the gastrointestinal tract . . . [t]hese pharmaceutical agents are, therefore, generally administered via intravenous or intramuscular routes, . . . entailing considerable discomfort . . . and even requiring administration in a hospital setting . . . in the case of certain IV infusions." Broder, column 1, lines 29-39. According to Broder, "certain agents which [ ] inhibit P-glycoprotein drug transport activity, particularly cyclosporins, can be used to increase substantially the oral bioavailability of otherwise poorly available or non-available pharmaceutical agents" (id., column 4, lines 13-17).

Broder specifically mentions paclitaxel and docetaxel[2] among a number of "antitumor agents which heretofore were administered only parenterally"[3] that "can now be administered . . . by the oral route with sufficient bioavailability to provide . . . blood concentrations which will be particularly effective in the treatment of patients with primary tumors and metastases" (id., column 15, lines 52-57). Broder "also comprehends

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[1] Broder et al., U.S. Patent 6,245,805, issued June 12, 2001

[2] According to Broder, "[d]ocetaxel has become commercially available as TAXOTERE® in parenteral form for the treatment of breast cancer." Broder, column 10, lines 17-18.

[3] Parenteral administration is defined as "[b]y some other means than through the gastrointestinal tract or lungs; referring particularly to the introduction of substances into an organism; i.e., by intravenous, subcutaneous, intramuscular, or intramedullary injection." Illustrated Stedman's Medical Dictionary, 24th Edition, Waverly Press, Inc., Baltimore, MD (1982).

methods of treating mammalian patients afflicted with cancers, tumors, . . . and any other disease conditions responsive to paclitaxel, taxanes, docetaxel, etoposide, prodrugs and derivatives of all the foregoing . . . Among the types of carcinoma which may be treated particularly effectively with oral paclitaxel, docetaxel, other taxanes, and their prodrugs and derivatives, are hepatocellular carcinoma and liver metastases, and cancers of the gastrointestinal tract, pancreas and lung" (id., column 15, lines 32-44).

Claim 7, which represents the claimed invention in its broadest aspect, requires intravenous administration of docetaxel to a patient with hepatocellular carcinoma. According to the examiner, "there are not enough blaze marks [in Broder] to conclude that the invention of claim 7 is anticipated" (Examiner's Answer, page 4), but claim 7 is nevertheless unpatentable because "Broder [ ] discloses (col. 9, lines 1-12) that docetaxel ("heretofore administered only parenterally") is useful for treating hepatocellular carcinoma and liver metastasis (col. 15, line 43)" (id., page 3).

The only differences between Broder and the claimed invention identified by the examiner concern limitations appearing only in claims dependent on claim 7. If we understand the examiner's reason for concluding that claim 7 is unpatentable, then, it is that Broder provides evidence that docetaxel was already known in the art to be "useful for treating hepatocellular carcinoma" parenterally at the time of the invention (id.).

Nevertheless, in our view, the examiner's interpretation of Broder's teachings goes too far. "A rejection based on section 103 clearly must rest on a factual basis, and these facts must be interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, all facts must be considered. The Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because it may

doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis. To the extent the Patent Office rulings are so supported, there is no basis for resolving doubts against their correctness. Likewise, we may not resolve doubts in favor of the Patent Office determination when there are deficiencies in the record as to the necessary factual bases supporting its legal conclusion of obviousness." In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968) (emphasis in original).

In our view, there are significant deficiencies and/or ambiguities in Broder's disclosure when the reference is considered in its entirety. As discussed above, the basis of the examiner's rejection appears to be that Broder provides evidence that it was already known in the art that hepatocellular carcinoma could be treated with parenterally administered docetaxel. The examiner's interpretation of the reference appears to be largely based on Broder's assertions that his method may be used to treat "any [ ] disease conditions responsive to paclitaxel, taxanes, docetaxel, [etc.]" (Broder, column 15, lines 32-37) and that "hepatocellular carcinoma and liver metastases" are "among the types of carcinoma which may be treated effectively with oral paclitaxel, docetaxel, other taxanes, [etc.]" (id., lines 40-43, emphasis ours).

Nevertheless, Broder does not explicitly teach that parenterally administered docetaxel was known to be useful in treating hepatocellular carcinoma. Moreover, Broder teaches that oral administration of paclitaxel (and by extension, docetaxel), together with an MDR inhibitor, results in a much higher level of the antitumor agent in the liver than is possible with IV infusion:

> The active ingredients will penetrate the gut wall as a result of the prior and/or concomitant administration of the MDR inhibitors . . . and will be taken up by the portal circulation rapidly, providing a higher local initial concentration of the chemotherapeutic agents in the liver (a far higher local concentration than is currently achieved with IV infusion therapy) than in the general systemic circulation or in most other organs at seven days. Furthermore, . . . the higher levels of paclitaxel in the liver after oral administration may not be reflected in increased plasma levels because of the high first pass effect of the liver . . . [I]n selectively producing high blood concentrations of antitumor agents, [the method] is particularly valuable in the treatment of liver cancers (e.g., hepatocellular carcinoma and liver metastases), gastrointestinal cancers (e.g., colon, rectal) and lung cancers.

Id., column 15, line 52 to column 16, line 6.

> Apart from the higher than previously achieved local concentration of the active ingredients in the liver, the plasma and tissue distribution of the active target agents administered orally with the [ ] enhancing agents . . . [is] similar to that observed upon IV administration.

Id., column 16, lines 28-33.

In our view, a reasonable inference is that selective concentration of the antitumor agent in the liver, a consequence of Broder's particular method of administration, is what makes these antitumor agents "valuable in the treatment of liver cancers" (id., column 16, lines 3-4). That being the case, we agree with appellants that "Broder's passing comments . . . that taxanes have previously been administered parenterally cannot sustain an argument that Broder somehow discloses parenteral (intravenous) use of docetaxel specifically in the treatment of hepatocellular cancer" (Reply Brief, page 4).

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir.

1993). On this record, we find that the examiner's initial burden[4] of providing the evidence necessary to establish a prima facie case of unpatentability has not been met. Accordingly, the rejection of claims 7-9, 12 and 16-22 under 35 U.S.C. § 103 is reversed.

REVERSED

Toni R. Scheiner )
Administrative Patent Judge )
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Donald E. Adams ) BOARD OF PATENT
Administrative Patent Judge ) APPEALS AND
)
) INTERFERENCES
)
Lora M. Green )
Administrative Patent Judge )

[4] The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

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